and duration are under-reported by patients and therefore impossible to completely exclude from any estimate of the association between the two diseases which are both strongly related to smoking.

Although we accept that our study does not completely exclude an independent effect of COPD on the risk of lung cancer, our own opinion is that the remaining association can be explained by residual confounding and that any truly independent effect would be very small, and certainly lower than a twofold increase. The importance of our interpretation lies in the allocation of resources in lung cancer research, which we believe should not be focused on the pursuit of a potential molecular link, but rather on early detection, novel and improved treatments, and smoking cessation.

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Balancing Radiation Pneumonitis Versus Locoregional Tumor Control in Non–Small-Cell Lung Cancer

To the Editor:

With great interest, we read the recent publication by Vinogradskiy et al.[1] The authors apply their radiation pneumonitis prediction model combining dose-volume and genetic components (single-nucleotide polymorphisms [SNPs]) for isotoxic mean lung dose determination. The five SNPs were found to predict for radiation pneumonitis and interestingly, they do not directly relate to lung injury, but rather to cellular repair and the tumor microenvironment.

The authors state that radiation pneumonitis is the dominant dose-limiting constraint in thoracic radiotherapy. This may have been the case for the cohort studied for 19% of the patients, mostly treated with three-dimensional conformal radiotherapy developed radiation pneumonitis of grade 3 or higher. With the introduction of highly conformal radiotherapy delivery techniques and by abandoning elective nodal irradiation, acute grade 3 esophagitis is increasingly the dose-limiting toxicity based both on clinical experience[2] and in silico studies.[3] As opposed to radiation pneumonitis, this burdensome side effect is not fatal but gradually develops during the course of (chemo)radiotherapy, lasting for several weeks thereafter necessitating analgesic medication and dietary alterations in the majority of patients. Moreover, late esophageal sequelae may develop, adversely influencing the patients' quality of life.

Vinogradskiy et al.[1] found that on the basis of the isotoxic physico-genetic model a reduction in prescribed dose would be necessary in 26 of the 141 patients studied. All but one of these patients belonged to the cohort that developed radiation pneumonitis. The mean clinically prescribed dose to this pneumonitis population was 64.7 Gy as opposed to 51.8 Gy predicted to be safe by the model. For a subset of the remaining patients, the dose could be slightly increased or decreased. This finding is intriguing keeping in mind that dose escalation in lung radiotherapy is thought to substantially increase local tumor control and ultimately survival.[4] Instead of decreasing the dose to prevent patients from developing unwanted side effects, more tailored solutions are feasible. van Baardwijk et al.[5] successfully pioneered an individualized approach escalating dose to maximal tolerance while keeping within the normal-tissue constraints, both theoretically and clinically. Both acute and late toxicity were acceptable. Additionally, MAASTRO clinic is currently conducting a randomized phase II trial including 18F-fluorodeoxyglucose-positron emission tomography information for tumor (subvolume) boosting (NCT01024829). On the basis of a recent in silico study,[3] Radboud University Nijmegen Medical Centre is carrying out the Individualized Dose Escalation in Advanced stage non-small cell Lung cancer using Volumetric Modulated Arc Therapy (IDEAL-VMAT) study (NCT01577212), whereby the irradiation dose is increased on an individual basis, taking into account multiple normal-tissue constraints.

For patients with both an unfavorable genetic profile and dose distribution, the radiation dose that can be safely administered on the basis of the proposed model is probably not curative. Therefore, the treating radiation oncologist may opt for a palliative protocol thereby decelerating tumor progression and alleviating tumor-associated complaints while preventing patients from unnecessary treatment-related side effects.

In summary, this article on model-based prescription provides new, yet prospectively unvalidated, tools for individualized dose-prescription in non–small-cell lung cancer patients. Radiation oncologists are encouraged to enhance radiation dose in patients with a favorable profile while seeking alternative therapeutic options in the remaining patients.

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Two Rare Exon 21 *EGFR* Mutations in Patients Treated with Gefitinib

To the Editor:

Treatment of non–small-cell lung cancer patients with reversible inhibitors of the tyrosine kinase domain of epidermal growth factor receptor (EGFR), gefitinib and erlotinib, in patients with *EGFR* mutations result in 70% to 80% responses.[1,2] Ninety percent of these consist of deletions of exon 19 and p.L858R mutations on exon 21.[2] However, through diverse mechanisms[3] resistance will eventually appear. There are also a minority of infrequent *EGFR* mutations at diagnosis whose predictive role is poorly characterized.[4]

We present two cases of patients diagnosed with a lung adenocarcinoma harboring rare *EGFR* mutations that received treatment with gefitinib. Mutational analysis was performed by polymerase chain reaction amplification of exons 18, 19, 20 and 21 of the *EGFR* gene and exon 1 of the *KRAS* gene followed by direct sequencing using BigDye 3.1 (Applied Biosystems, Foster City, CA) and analysis in a Genetic Analyzer 3500Dx (Applied Biosystems).

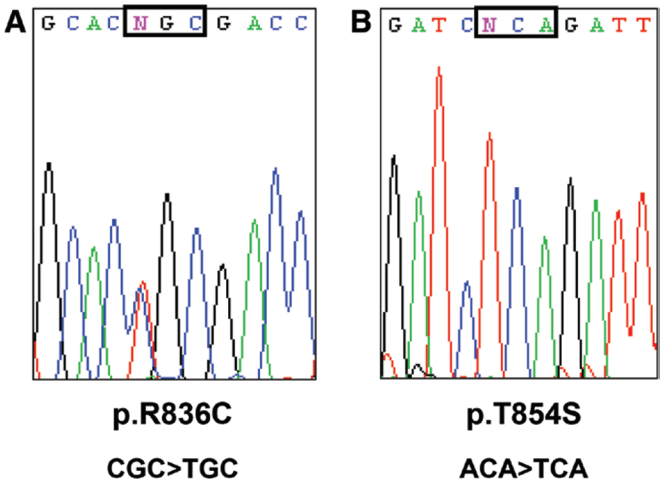

FIGURE 1. Sequencing chromatograms showing EGFR mutations affecting cases 1 and 2. *A,* Case 1-arginine(R) to cysteine (C) substitution at amino acid position 836 (p.R836C) resulting from a CGC→TGC exchange. *B,* Case 2-threonine (T) to serine (S) substitution at amino acid position 854 (p.T854S) resulting from a ACA→TCA exchange.

CASE 1

A white, 81-year-old, male exsmoker was diagnosed in July 2010 of a stage IIIA (T4N0M0) lung adenocarcinoma. Molecular analysis demonstrated the presence of a p.R836C mutation in exon 21 of the *EGFR* gene. He began first-line chemotherapy with a platinum doublet. Response assessment by computed tomography scan showed stabilization. However, because of symptomatic progression he started treatment with gefitinib 250 mg/day. In January 2011 he was admitted in hospital because of increasing dyspnoea and pain. The computed tomography scan showed progression of the tumor with appearance of pleural effusion. The study of the fluid confirmed the diagnosis of metastasis from adenocarcinoma harboring the p.R836C mutation on exon 21 (Fig. 1A). No p.T790M mutation on exon 20 or hepatocyte growth factor receptor (MET) amplification was detected. Progressive disease led to rapid deterioration of performance status and the patient died in early March 2011.

CASE 2

A white, 54-year-old, heavy smoker man was diagnosed in May 2011 with a lung adenocarcinoma stage IIIB (T4N2M0) not suitable for radical treatment. Evaluation of *EGFR* mutational status demonstrated the presence of the p.T854S mutation in exon 21. No wild-type allele was detected in this position, indicating that the mutation was either hemizygous or homozygous (Fig. 1B). He started treatment with gefitinib and early (6 weeks) assessment by computerized tomography demonstrated progressive disease. He received subsequent lines of treatment with stable disease as best response. Local and central nervous system progression led

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